

<p>(19)  <b>Canadian Intellectual Property Office</b></p> <p>An Agency of Industry Canada</p>	<p><b>Office de la Propriété Intellectuelle du Canada</b></p> <p>Un organisme d'Industrie Canada</p>	<p>(11) <b>CA 2 318 960</b></p> <p>(40) 05.08.1999</p> <p>(43) 05.08.1999</p>	<p>(13) <b>A1</b></p>
--	--	---	-----------------------

(12)

(21) **2 318 960**

(51) Int. Cl.<sup>6</sup>: **A61K 31/135**

(22) **28.01.1999**

(85) **25.07.2000**

(86) **PCT/US99/01952**

(87) **WO99/38502**

(30) **60/072,955 US 29.01.1998**

(72) **YOUNG, JAMES W. (US).**

(71) **SEPRACOR INC.,  
111 Locke Drive, MARLBOROUGH, XX (US).**

(74) **OSLER, HOSKIN & HARCOURT LLP**

(54) **UTILISATIONS PHARMACEUTIQUES DE (+)-BUPROPION OPTIQUEMENT PUR**  
 (54) **PHARMACEUTICAL USES OF OPTICALLY PURE (+)-BUPROPION**

(57)

Methods and compositions are disclosed utilizing the optically pure (+)-isomer of bupropion, which is a potent drug for treating depression, Parkinson's disease, obesity, weight gain, bipolar, attention-deficit or conduct disorders, psychosexual dysfunction, bulimia, eating disorders or specific food craving. The composition can be administered intravenously, transdermally (patch) or orally, possibly in a sustained release form.

O P I C  
OFFICE DE LA PROPRIÉTÉ  
INTELLECTUELLE DU CANADA



C I P O  
CANADIAN INTELLECTUAL  
PROPERTY OFFICE

(12) (19) (CA) **Demande-Application**

(21) (A1) **2,318,960**  
(86) 1999/01/28  
(87) 1999/08/05

(72) YOUNG, JAMES W., US

(71) SEPRACOR INC., US

(51) Int.Cl.<sup>6</sup> A61K 31/135

(30) 1998/01/29 (60/072,955) US

(54) **UTILISATIONS PHARMACEUTIQUES DE (+)-BUPROPION  
OPTIQUEMENT PUR**

(54) **PHARMACEUTICAL USES OF OPTICALLY PURE  
(+)-BUPROPION**

(57) La présente invention concerne des procédés et des compositions utilisant l'isomère (+) optiquement pur de bupropion, qui est un médicament puissant pour le traitement des dépressions, de la maladie de Parkinson, de l'obésité, de la prise de poids, des maladies à forme bipolaire, des troubles déficitaires de l'attention ou des troubles de conduite, des dysfonctionnements psychosexuels, de la boulimie, des troubles de l'alimentation ou d'une appétence de nourriture spécifique. Une telle composition peut être administrée par voie intraveineuse, par voie transdermique (timbre) ou par voie orale, éventuellement sous une forme à libération prolongée.

(57) Methods and compositions are disclosed utilizing the optically pure (+)-isomer of bupropion, which is a potent drug for treating depression, Parkinson's disease, obesity, weight gain, bipolar, attention-deficit or conduct disorders, psychosexual dysfunction, bulimia, eating disorders or specific food craving. The composition can be administered intravenously, transdermally (patch) or orally, possibly in a sustained release form.



Industrie Canada Industry Canada

CA 02318960 2000-07-25

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification 6 :</b> <b>A61K 31/135</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/38502</b> <b>(43) International Publication Date:</b> 5 August 1999 (05.08.99)
<b>(21) International Application Number:</b> PCT/US99/01952 <b>(22) International Filing Date:</b> 28 January 1999 (28.01.99) <b>(30) Priority Data:</b> 60/072,955 29 January 1998 (29.01.98) US <b>(71) Applicant:</b> SEPRACOR INC. [US/US]; 111 Locke Drive, Marlborough, MA 01752 (US). <b>(72) Inventor:</b> YOUNG, James, W.; 765 Talisman Court, Palo Alto, CA 94303 (US). <b>(74) Agents:</b> LAWRENCE, Stanton, T., III. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PHARMACEUTICAL USES OF OPTICALLY PURE (+)-BUPROPION <b>(57) Abstract</b> <p>Methods and compositions are disclosed utilizing the optically pure (+)-isomer of bupropion, which is a potent drug for treating depression, Parkinson's disease, obesity, weight gain, bipolar, attention-deficit or conduct disorders, psychosexual dysfunction, bulimia, eating disorders or specific food craving. The composition can be administered intravenously, transdermally (patch) or orally, possibly in a sustained release form.</p>		

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952

## PHARMACEUTICAL USES OF OPTICALLY PURE (+) -BUPROPION

1. FIELD OF THE INVENTION

5 This invention relates to methods of treatment and pharmaceutical compositions employing the compound (+)-bupropion.

2. BACKGROUND OF THE INVENTION10 2.1. STERIC RELATIONSHIPS AND DRUG ACTION

Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote  
15 the absolute configuration of the molecule about its chiral center(s). The prefixes (+) and (-) or d and l are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is  
20 dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric or  
25 racemic mixture.

Stereochemical purity is of importance in the field of pharmaceuticals, where 16 of the 20 most prescribed drugs exhibit chirality. A case in point is provided by the L-form of the  $\beta$ -adrenergic blocking agent, propranolol, which is  
30 known to be 100 times more potent than the D-enantiomer.

Furthermore, optical purity is important since certain isomers may actually be deleterious rather than simply inert. For example, it has been suggested that the D-enantiomer of thalidomide was a safe and effective sedative  
35 when prescribed for the control of morning sickness during pregnancy, while the corresponding L-enantiomer was a potent teratogen.

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

Bupropion is available only as a racemic mixture called Wellbutrin® and Wellbutrin SR® (for depression), and Zyban® (to achieve smoking cessation). That is, bupropion is available as a mixture of optical isomers, called

5 enantiomers. The racemic mixture of bupropion which is commercially available is administered as a hydrochloride salt. In addition, European Patent Application No. 84101070.5 published September 12, 1984 discloses the benefits of bupropion maleate over bupropion hydrochloride.

10 Bupropion is used primarily in the treatment of depression, which along with mania, falls under the heading of affective disorders. Particularly, bupropion is used in patients who do not respond to, or cannot tolerate other antidepressants, such as the tricyclic agents or monoamine

15 oxidase inhibitors. Additionally, the racemic mixture of bupropion is useful in the management of patients with bipolar and schizo-affective disorder, attention-deficit disorder, psycho-sexual dysfunction, bulimia and other eating disorders, and Parkinson's disease.

20 Affective disorders, including major depression, and the bipolar, manic-depressive illness, are characterized by changes in mood as the primary clinical manifestation. Major depression is the most common of the significant mental illnesses, and it must be distinguished clinically from

25 periods of normal grief, sadness and disappointment, and the related dysphoria or demoralization frequently associated with medical illness. Depression is characterized by feelings of intense sadness, and despair, mental slowing and loss of concentration, pessimistic worry, agitation, and

30 self-deprecation. Physical changes can also occur, including insomnia, anorexia, and weight loss, decreased energy and libido, and disruption of hormonal circadian rhythms. Often the condition responds well to tricyclic or related antidepressant drugs, monoamine oxidase inhibitors, or in

35 resistant cases or severe disease, to electro-convulsive shock treatment.

- 2 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952

Mania, as well as depression, is characterized by changes in mood as the primary symptom. Either of these two extremes of mood may be accompanied by psychosis with disordered thought and delusional perceptions. Psychosis may have, as a secondary symptom, a change in mood, and it is this overlap with depression that causes much confusion in diagnosis. Severe mood changes without psychosis frequently occur in depression and are often accompanied by anxiety.

Through an unknown mechanism of action, bupropion has been demonstrated to be an effective treatment in depression in short-term and longer duration clinical studies. The racemic mixture of bupropion has been reported to have an antidepressant activity equal to amitriptyline, the tricyclic antidepressant, with fewer anticholinergic, sedative and cardiovascular side effects than with amitriptyline.

Parkinson's disease, independent of a specific etiology, is a chronic, progressive central nervous system disorder which usually appears insidiously in the latter decades of life. The disease produces a slowly increasing disability in purposeful movement. It is characterized by four major clinical features of tremor, bradykinesia, rigidity and a disturbance of posture. Often patients have an accompanying dementia. In idiopathic Parkinsonism, there is usually a loss of cells in the substantia nigra, locus ceruleus, and other pigmented neurons of the brain, and a decrease of dopamine content in nerve axon terminals of cells projecting from the substantia nigra. The understanding that Parkinsonism is a syndrome of dopamine deficiency and the discovery of levodopa as an important drug for the treatment of the disease were the logical culmination of a series of related basic and clinical observations, which serves as the rationale for drug treatment.

When the racemic mixture of bupropion is used to treat Parkinson's disease, an improvement in gait, akinesia, and postural stability were observed, with tremor improving in those patients experiencing the most global benefit.

- 3 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

Concomitant depression was alleviated in several of the patients reporting the condition.

Attention-deficit disorder ("ADD") is a common behavioral learning disorder in children which adversely affects school performance and family relationships. Symptoms and signs include hyperactivity (e.g., ADDH and AD/HD, DSM-IV), impulsivity, emotional lability, motor incoordination and some perceptual difficulties. Treatment has included psychostimulants, which while effective are controversial, and may cause troubling side effects such as dysphoria, headache and growth retardation. Other drugs, including the tricyclic antidepressants, appear to improve attention, but may be less effective than the psychostimulants.

Bupropion has been shown to be effective in children with attention-deficit disorder or conduct disorder thus improving the symptoms of anxiety, hostility and uncooperativeness, antisocial behavior, as well as eating disturbances. The drug has also demonstrated activity in cases of psycho-sexual dysfunction and bulimia. However, bupropion is contra-indicated in patients with a seizure disorder, or a current or prior diagnosis of bulimia or anorexia nervosa characterized by a disturbed sense of body image and abnormally high anxiety about weight gain.

It has been suggested that the racemic mixture of bupropion could be used to assist in weight loss. Treatment with bupropion is consistently associated with a lack of weight gain. Also bupropion reduces episodes of binge eating and purging. Although the mechanism by which bupropion causes weight loss is uncertain, an increase in the activity of the patient may play some part together with subtle changes in food intake and metabolism.

The causes of excess body weight and/or obesity are complex; however, a common denominator in the overweight person's diet is a caloric intake which exceeds that person's body expenditures. One method of treating a person who is overweight and/or obese is to restrict that person's caloric

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

intake, in combination with an exercise regimen. This method may be limited in its effectiveness since many overweight or obese people have developed eating and activity patterns which are counterproductive to achieving weight reduction.

5 Another method to treat overweight or obese patients is to administer appetite suppressant drugs in conjunction with a weight reduction program. The drawback to this method is that many appetite suppressant drugs produce undesirable adverse effects which limit their usefulness.

10 The racemic mixture of bupropion, in addition to its use in the treatment of depression and the other above-mentioned disorders, has been shown to have a wide spectrum of action which includes:

- 15 -- Treatment of the effects of ethanol (U.S. Patent No. 4,393,078)
- Treatment of Tardive Dyskinesia (U.S. Patent No. 4,425,363)
- Treatment of Minimal Brain Dysfunction (U.S. Patent No. 4,435,449)
- 20 -- Treatment of amelioration of prostate hypertrophy and sexual dysfunction (U.S. Patent No. 4,835,147)
- Treatment of psychostimulant addiction (U.S. Patent No. 4,935,429)
- 25 -- Treatment of Psychosexual Dysfunction (U.S. Patent No. 4,507,323)
- Methods of Reducing Cholesterol (U.S. Patent No. 4,438,138)
- 30 -- Methods of assisting weight loss (U.S. Patent No. 4,895,845)

The racemic mixture of bupropion has been shown to have certain advantages over other antidepressant drugs. For example, bupropion does not inhibit monoamine oxidase, or block the reuptake of serotonin. At therapeutic  
35 concentrations, the compound presumably does not bind to adrenergic, dopamine, GABA, histamine, muscarinic, serotonin, or imipramine binding sites. While its specific

- 5 -

SUBSTITUTE SHEET ( rule 26 )



CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

neurochemical antidepressant action is unknown, it does have a relatively weak effect on blocking the reuptake of dopamine, and it appears to reduce norepinephrine metabolism.

While the racemic mixture of bupropion has 5 advantages, it also has disadvantages. Among these disadvantages are adverse effects in addition to those described above. The most serious adverse effect associated with the racemic mixture of bupropion is the increased incidence of seizures. In addition, other frequently 10 reported adverse effects associated with the use of racemic bupropion include nausea, vomiting, excitement, agitation, blurred vision, restlessness, postural tremor, and some hallucinations/confusional states with the potential for abuse. Other adverse or side effects associated with the 15 racemic mixture of bupropion include but are not limited to anxiety, insomnia, headaches and/or migraines, dry mouth, constipation, tremor, sleeping disturbances, dermatologic problems (e.g., rashes), neuropsychiatric signs and symptoms (e.g., delusions and paranoia), and weight loss or gain. 20 See, the Physician's Desk Reference® (1998). These effects are dose limiting in a number of patients. In Parkinsonian patients, the adverse effects can be the particular toxicity of the racemic mixture of bupropion or the result of a drug interaction (as most patients were receiving concomitant 25 levodopa).

Thus, it is desirable to find a compound with the advantages of the racemic mixture of bupropion without the above-described disadvantages.

30

35

- 6 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

### 3. SUMMARY OF THE INVENTION

The active compound of compositions and methods disclosed herein is an optical isomer of the compound bupropion which is described in United States Patent Nos. 5 3,819,706 and 3,885,046. Chemically, this isomer is (+)-2-(tertbutylamino)-3'-chloropropiophenone or (+)-1-(3-chlorophenyl)-2[(1,1-dimethyl-ethyl)amino]-1-propanone. This isomer will hereinafter be referred to as "(+)-bupropion", which also includes the substantially optically pure (+)-  
10 bupropion isomer.

It has now been discovered that the optically pure (+)-isomer of bupropion is an effective antidepressant which is useful in treating depression in humans. In accordance with the present invention, (+)-bupropion can be used to  
15 treat depression while avoiding adverse effects including but not limited to seizures, agitation, dry mouth, insomnia, headache/migraine, nausea, dizziness, tachycardia, vomiting, constipation, and tremor associated with the racemic mixture of bupropion. It has also been discovered that (+)-bupropion  
20 and pharmaceutical compositions containing optically pure (+)-bupropion are useful in treating weight gain or obesity. Furthermore, it has been discovered that the optically pure (+)-isomer of bupropion is useful in the treatment of Parkinson's disease. In addition, it has been found that the  
25 optically pure (+)-isomer is useful in the treatment of other disorders including but not limited to bipolar disorders, attention-deficit disorders, conduct disorders, psycho-sexual dysfunction, bulimia, eating disorders and specific food cravings.

30 The present invention also includes methods for treating the above-described conditions in a human while avoiding adverse effects that are associated with the racemic mixture of bupropion, by administering the optically pure (+)-isomer of bupropion to said human.  
35

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

#### 4. DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of treating depression in a human while avoiding the concomitant liability of adverse effects associated with the administration of racemic bupropion which comprises administering to said human in need of antidepressant therapy, an amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, said amount being sufficient to alleviate depression, but insufficient to cause adverse effects associated with racemic bupropion.

The present invention also encompasses pharmaceutical compositions for the treatment of humans which comprises a therapeutically effective amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, and a pharmaceutically acceptable carrier. Preferred pharmaceutical compositions are those which have a means for controlled sustained release of the active ingredient, (+)-bupropion.

The present invention further encompasses a method of treating Parkinson's disease in a human while avoiding the concomitant liability of adverse effects associated with the administration of racemic bupropion, which comprises administering to said human suffering from Parkinson's disease, an amount of (+)-bupropion, or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, said amount being sufficient to alleviate said condition, but insufficient to cause adverse effects associated with administration of racemic bupropion.

Further, the present invention encompasses a method of treating obesity or weight gain in a human, which comprises administering to said human in need of a reduction in weight, an amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, said amount being sufficient to reduce weight or prevent weight gain, but insufficient to cause adverse effects associated with administration of racemic bupropion.

- 8 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

The present invention also encompasses a method of treating disorders including, but not limited to, bipolar disorders, attention-deficit disorders, conduct disorders, psycho-sexual dysfunction, bulimia, eating disorders and 5 specific food cravings in humans while avoiding the concomitant liability of adverse affects associated with the administration of racemic bupropion, which comprises administering to a human in need of such therapy a therapeutically effective amount of (+)-bupropion, or a 10 pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer.

The racemic mixture of bupropion (i.e., approximately a 50:50 mixture of its two enantiomers) causes antidepressant activity and provides therapy and/or reduction 15 of symptoms in a variety of conditions and disorders; however, this racemic mixture, while offering the expectation of efficacy, causes a broad range of adverse effects. Utilizing the optically pure (+)-isomer of bupropion results in clearer dose-related definitions of efficacy, diminished 20 adverse effects, and accordingly an improved therapeutic index. It is therefore, more desirable to use the (+)-isomer of bupropion for the conditions described herein.

The term "adverse effects" as used herein includes, but is not limited to seizures, dry mouth, insomnia, 25 dizziness, restlessness, anxiety, agitation, headache/migraine, nausea/vomiting, constipation, tremor, delusions, tachycardia, hallucinations, psychotic episodes, blurred vision, confusion, paranoia, rashes and sleep disturbances.

30 The term "substantially free of the (-)-stereoisomer" as used herein means that the composition contains a greater proportion of the (+)-isomer of bupropion in relation to the (-)-isomer of bupropion. In a preferred embodiment the term "substantially free of its (-)-isomer" as 35 used herein means that the composition contains at least 90% by weight of (+)-bupropion and 10% by weight or less of (-)-bupropion; or more preferably about 95% by weight of (+)-

- 9 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

bupropion and 5% or less of its (-)-isomer. These percentages are based on the total amount of bupropion present in the composition. In the most preferred embodiment the term "substantially free of the (-)-stereoisomer" means  
5 that the composition contains approximately 99% by weight of (+)-bupropion, and 1% or less of the (-)-bupropion. In another preferred embodiment, the term "substantially free of its (+)-stereoisomer" as used herein means that the composition contains greater than 99% by weight of the (+)-  
10 isomer of bupropion, again based on the total amount of bupropion present. The terms "substantially optically pure (+)-isomer of bupropion," "optically pure (+)-isomer of bupropion" and "(+)-isomer of bupropion" are also encompassed by the above-described amounts.

15 The term "a method of treating depression" as used herein means relief from the symptoms of depression which include, but are not limited to changes in mood, feelings of intense sadness and despair, mental slowing, loss of concentration, pessimistic worry, agitation, and self-  
20 deprecation. Physical changes may also be relieved, including insomnia, anorexia and weight loss, decreased energy and libido, and the return of normal hormonal circadian rhythms.

The term "attention deficit disorder" (ADD) and  
25 "attention deficit disorder with hyperactivity" (ADHD), DSM-III, or attention deficit/hyperactivity disorder (AD/HD), DSM-IV are used herein mean in accordance with the accepted meanings.

The term "treating Parkinson's disease" as used  
30 herein means relief from the symptoms of Parkinson's disease which include, but are not limited to tremor, bradykinesia, rigidity, and a disturbance of posture.

The term "treating obesity or weight gain in a human" as used herein means reduction of weight or relief  
35 from being overweight or gaining weight due to extensive consumption of food and other factors including metabolism disorders.

- 10 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

#### 4.1. SYNTHESIS OF OPTICALLY PURE BUPROPION

The synthesis of the (+)-isomer of bupropion may start from readily available 3-chloropropiophenone (1).  
5 Reaction of (1) with a (2S,3S)-(-)-dialkyl tartrate such as (-)-dimethyl or diethyl tartrate in the presence of an acid catalyst such as methanesulfonic acid gives the chiral acetal (2) according to Castaldi (G. Castaldi, et al., *J. Org. Chem.* 1987, 52: 3018). Stereoselective bromination with bromine in  
10 carbon tetrachloride (or alternatively in ethyl acetate) then produces the corresponding bromoacetal (3) as the major product according to the above-referenced procedure developed by Castaldi and co-workers. The bromoacetal (3) is purified by column chromatography to yield the optically pure  
15 bromoacetal (3) which is then hydrolyzed in the presence of an acid to afford the bromoketone (4). Treatment of the bromoketone (4) with tert-butylamine, followed by reaction with anhydrous hydrogen chloride, then produces optically pure (+)-bupropion hydrochloride (5) after recrystallization.  
20 See the scheme below.

25

30

35

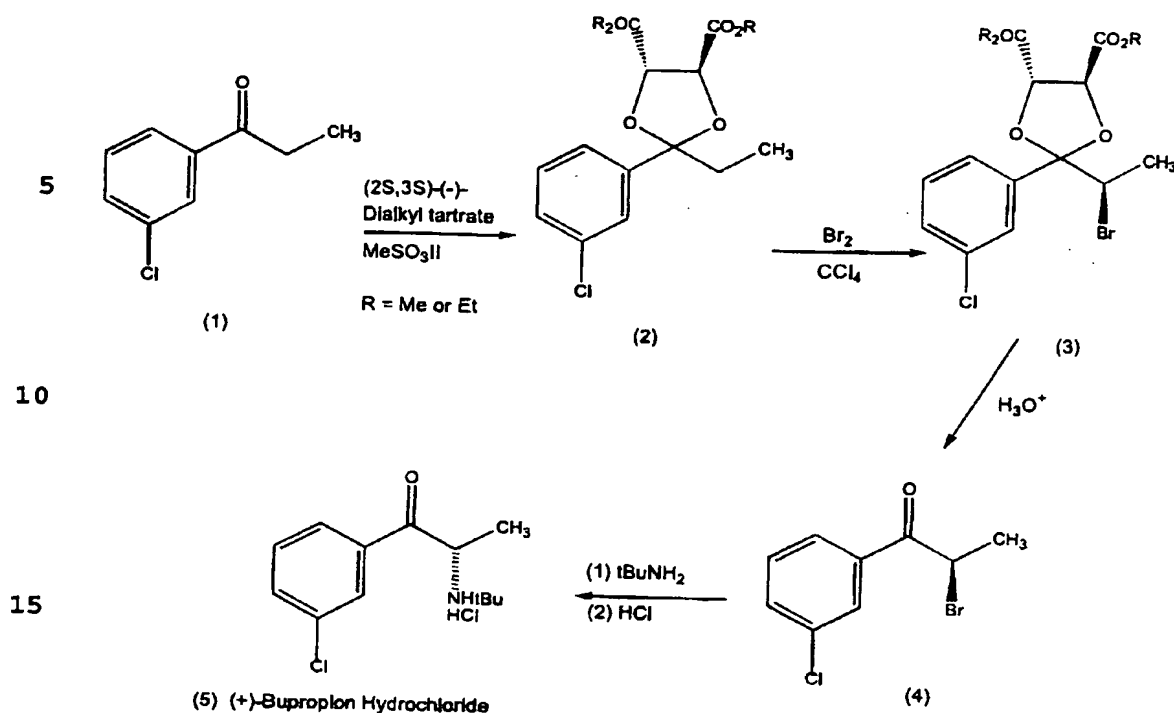
- 11 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952



20 Alternatively, the optically pure isomers of bupropion can be prepared by another asymmetric route according to the procedures reported by Musso et al., "Synthesis and Evaluation of the Antidepressant Activity of the Enantiomers of Bupropion", *Chirality* 5:495-500 (1993) which is incorporated herein by reference in its entirety.

25 In addition to the above-described methods the stereoisomers of bupropion may be obtained by resolutions of a mixture of enantiomers of bupropion using conventional means such as an optically active resolving agent; see, for example, "Stereochemistry of Carbon Compounds", by E.L. Eliel (McGraw-Hill, NY, 1962), and S.H. Wilen, p. 268 in "Tables of Resolving Agents and Optical Resolutions" (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

30 The magnitude of a prophylactic or therapeutic dose of (+)-bupropion in the acute or chronic management of disease will vary with the severity of the condition to be treated and its route of administration. The dose and dose

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

frequency will also vary according to the age, weight, condition and response of the individual patient. In general, the recommended daily dose range for the conditions described herein lies within the range of from about 10 mg to 5 about 750 mg per day, generally divided equally into doses given three or four times a day. Preferably, a daily dose range should be between 50 mg and 600 mg per day, usually divided equally into a three or four times a day dosing. Most preferably, a daily dose range should be between 60 mg 10 and 450 mg per day, usually divided equally into a three times or a four times a day dosing. It may be necessary to use dosages outside these ranges in some cases. The physician will know how to increase, decrease or interrupt treatment based upon patient response. The various terms 15 described above such as "said amount being sufficient to alleviate said depression", "said amount being sufficient to alleviate said condition" when said condition is Parkinson's Disease, "said amount being sufficient to reduce weight or weight gain", "said amount being sufficient to achieve weight 20 loss" and "therapeutically effective amount" are encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage 25 of (+)-bupropion. For example, oral, rectal, parenteral, transdermal, subcutaneous, intrathecal, intramuscular and the like may be employed as appropriate. Dosage forms include tablets, coated tablets, caplets, capsules, troches, dispersions, sustained release formulations, suspensions, 30 solutions, patches and the like.

The pharmaceutical compositions of the present invention comprise the (+)-isomer of bupropion as active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and 35 optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared



CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids.

Since the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable  
5 non-toxic acids including inorganic and organic acids. Such acids include maleic, acetic, benzene-sulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic,  
10 nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are hydrobromic, hydrochloric, phosphoric, and sulfuric acids.

The pharmaceutical compositions of the present  
15 invention include compositions suitable for oral, rectal, and parenteral administration (including subcutaneous, intrathecal, intramuscular, and intravenous), although the most suitable route in any given case will depend on the nature and severity of the condition being treated. The most  
20 preferred route of the present invention is the oral route. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In the case where an oral composition is employed,  
25 a suitable dosage range for use is, e.g., from about 10 mg to about 750 mg per day, generally divided equally into a three times a day dosing, preferably from about 50 mg to about 600 mg per day, generally divided equally into a three times a day dosing and most preferably from about 60 mg to about 450  
30 mg per day, generally divided equally into a three times a day dosing. Patients may be upward titrated from below to within this dose range to a satisfactory control of symptoms, or blood pressure as appropriate.

In practical use, (+)-bupropion can be combined as  
35 the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take

- 14 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous injections or infusions). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, for example, suspensions, elixirs and solutions; or aerosols; or carriers such as starches, sugars, microcrystalline cellulose, stabilizers, diluents, granulating agents, lubricants, binders, fillers, disintegrating agents and the like in the case of oral solid preparations such as, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. The preferred solid oral preparation is tablets. The most preferred solid oral preparation is coated tablets. Because of their ease of administration tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

Pharmaceutical stabilizers may also be used to stabilize compositions containing (+)-bupropion or salts thereof; acceptable stabilizers including but are not limited to L-cysteine hydrochloride, glycine hydrochloride, malic acid, sodium metabsulfite, citric acid, tartaric acid and L-cystine dihydrochloride. See, e.g., U.S. Patent No. 5,358,970 which is incorporated herein by reference.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release or sustained release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200, 4,008,719, 4,687,660, and 4,769,027, the disclosures of which are hereby incorporated by reference. Preferred controlled release or sustained released tablets

- 15 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

for use with (+)-bupropion are described in U.S. Patent No. 5,427,798 which is incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented  
5 as discrete units such as capsules, cachets, or tablets or aerosol sprays, each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion.  
10 Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately  
15 admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients.  
20 Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, filler, lubricant, inert diluent, and/or surface active or dispersing agent. Molded tablets may be made by molding in a  
25 suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 10 mg to about 250 mg of the active ingredient, and each cachet or capsule contains from about 10 mg to about 250 mg of the active ingredient. Most  
30 preferably, the tablet, cachet or capsule contains one of four dosages: about 50 mg, about 75 mg, about 100 mg and about 150 mg of active ingredient.

The invention is further defined by reference to the following examples describing in detail the preparation  
35 of the compound and compositions of the present invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be

- 16 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

practiced without departing from the purpose and interest of this invention.

All temperatures are in degrees Celsius.

5

## 5. EXAMPLES

### 5.1. EXAMPLE 1

#### ORAL FORMULATION

#### Coated Tablets:

10 Formula	Quantity per Tablet (mg.)
(+) -bupropion	75
Lactose	125
Corn Starch	5.0
15 Water (per thousand Tablets)	30.0 ml *
Magnesium Stearate	0.5
Corn Starch	25.0

\*

20 The water evaporates during manufacture.

The active ingredient is blended with the lactose until a uniform blend is formed. The smaller quantity of corn starch is blended with a suitable quantity of water to form a corn starch paste. This is then mixed with said uniform blend until a uniform wet mass is formed. The remaining corn starch is added to the resulting wet mass and mix until uniform granules are obtained. The granules are then screened through a suitable milling machine, using a 1/4 inch stainless steel screen. The milled granules are then dried in a suitable drying oven until the desired moisture content is obtained. The dried granules are then milled through a suitable milling machine using 1/4 mesh stainless steel screen. The magnesium stearate is then blended and the resulting mixture is compressed into tablets of desired shape, thickness, hardness and disintegration. Tablets are coated by standard aqueous or nonaqueous techniques.

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

**5.2. EXAMPLE 2**  
**ORAL FORMULATION**

**Capsules:**

5	Formula	Quantity per capsule in mg.		
		<u>A</u>	<u>B</u>	<u>C</u>
	Active ingredient	25	50	75
10	(+) -bupropion			
	Lactose	149.5	124.5	374
	Corn Starch	25	25	50
	Magnesium Stearate	0.5	0.5	1.0
	Compression Weight	200.0	200.0	500.0

15        The active ingredient, (+)-bupropion, lactose, and corn starch are blended until uniform; then the magnesium stearate is blended into the resulting powder. The resulting mixture is encapsulated into suitably sized two-piece hard gelatin capsules.

20

**5.3. EXAMPLE 3**  
**ORAL FORMULATION**

**Tablets**

25	Formula	Quantity per Tablet in mg.		
		<u>A</u>	<u>B</u>	<u>C</u>
	Active ingredient, (+) -bupropion	20	40	100
30	lactose BP	134.5	114.5	309.0
	starch BP	30.0	30.0	60.0
	Pregelatinized Maize Starch BP	15.0	15.0	30.0
	magnesium stearate	0.5	0.5	1.0
	Compression Weight	200.0	200.0	500.0

35        The active ingredient is sieved through a suitable sieve and blended with lactose, starch, and pregelatinized maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules

- 18 -

**SUBSTITUTE SHEET ( rule 26 )**

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952

are screened and blended with the magnesium stearate. The granules are then compressed into tablets using punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

#### 5.4. EXAMPLE 4

Sustained Release Formulation (Tablet)

10	FORMULA	QUANTITY PER TABLET (mg)
	(+) -bupropion hydrochloride	100
	Contramid® crosslinked amylose	98.8
	Cysteine hydrochloride	7.5
15	Magnesium stearate	1.2

(+) -Bupropion Hydrochloride is formulated using Contramid® (Labopharm, Inc, Quebec) technology. The formulation is prepared by blending the ingredients above (dry) and compressing into tablets. Alternatively, the ingredients can be formulated using wet granulation technology known in the art. (See Example 1).

#### 5.5. EXAMPLE 5

Sustained Release Formulation (Tablet)

25	FORMULA	QUANTITY PER TABLET (mg)
	Contramid® crosslinked amylose	98.8
	Cysteine hydrochloride	7.5
	(+) -bupropion hydrochloride	75
30	Magnesium stearate	1.2

(+) -Bupropion Hydrochloride is formulated using Contramid® (Labopharm, Inc, Quebec), technology. The formulation is prepared by blending the ingredients above (dry) and compressing into tablets. Alternatively, the ingredients can be formulated using wet granulation technology known in the art. (See Example 1).

- 19 -

**SUBSTITUTE SHEET ( rule 26 )**

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

5.6. EXAMPLE 6

	FORMULA	QUANTITY PER TABLET (mg)
	(+)-bupropion hydrochloride	150
5	Diffutab® hydrophilic polymer mixture	100
	Microcrystalline cellulose	100
	Cysteine hydrochloride	7.5
10	Magnesium stearate	4

(+)-Bupropion Hydrochloride is formulated using Diffutab® (Eurand, Microencapsulation, S.A. of Switzerland) technology. The formulation components are dry blended and directly compressed into tablets or formulated using wet granulation technology.

The embodiments of the present invention described above are intended to be merely exemplary and those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. All such equivalents are considered to be within the scope of the present invention and are covered by the following claims.

The contents of all references described herein are hereby incorporated by reference.

Other embodiments are within the following claims.

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952

What is claimed is:

1. A method of treating depression in a human while avoiding the concomitant liability of adverse effects associated with administration of racemic bupropion, which  
5 comprises administering to a human in need of antidepressant therapy, a therapeutically effective amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer.
- 10 2. The method of claim 1 wherein said amount is sufficient to alleviate said depression, but insufficient to cause said adverse effects associated with administration of racemic bupropion.
- 15 3. The method of claim 1 wherein (+)-bupropion is administered intravenously, transdermally or orally.
4. The method of claim 3 wherein (+)-bupropion is administered orally as a tablet or a capsule.
- 20 5. The method of claim 1 wherein the amount administered is from about 10 mg to about 750 mg.
6. The method of claim 5 wherein the amount  
25 administered is from about 50 mg to about 600 mg.
7. The method of claim 6 wherein the amount administered is from about 60 mg to about 450 mg.
- 30 8. The method of claim 1 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of bupropion.
- 35 9. The method of claim 1 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof,



CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

substantially free of its (-)-stereoisomer is administered together with a pharmaceutically acceptable carrier.

10. The method according to claim 1 wherein  
5 (+)-bupropion is administered as the hydrochloride salt.

11. The method of claim 1 wherein (+)-bupropion is administered in a sustained or controlled release formation.

10 12. A method of treating Parkinson's disease in a human while avoiding the concomitant liability of adverse effects associated with the administration of racemic bupropion, which comprises administering to said human in need of treatment for Parkinson's disease, a therapeutically  
15 effective amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer.

13. The method of claim 12, wherein said said amount  
20 is sufficient to alleviate said disease, but insufficient to cause said adverse effects associated with administration of racemic bupropion.

14. The method of claim 12 wherein (+)-bupropion is  
25 administered by intravenously, transdermally, or orally.

15. The method of claim 14 wherein (+)-bupropion is administered orally as a tablet or a capsule.

30 16. The method of claim 12 wherein the amount administered is from about 10 mg to about 750 mg.

17. The method of claim 16 wherein the amount administered is from about 50 mg to about 600 mg.

35 18. The method of claim 17 wherein the amount administered is from about 60 mg to about 450 mg.

- 22 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

19. The method of claim 12 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of bupropion.

5

20. The method of claim 12 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, is administered together with a pharmaceutically acceptable carrier.

10

21. The method according to claim 12 wherein (+)-bupropion is administered as the hydrochloride salt.

22. The method of claim 12 wherein (+)-bupropion is administered in a sustained or controlled release formulation.

23. A method for treating obesity or weight gain in a human which comprises administering to a human in need of weight reduction or weight control a therapeutically effective amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer

24. The method of claim 23 wherein said amount is sufficient to alleviate obesity or weight gain, but insufficient to cause adverse effects associated with administration of racemic bupropion.

25. The method of claim 23 wherein (+)-bupropion is administered by intravenously, transdermally, or orally.

26. The method of claim 25 wherein (+)-bupropion is administered orally as a tablet or a capsule.

35

27. The method of claim 23 wherein the amount administered is from about 10 mg to about 750 mg.

- 23 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952 -

28. The method of claim 27 wherein the amount administered is from about 50 mg to about 600 mg.

29. The method of claim 28 wherein the amount administered is from about 60 mg to about 450 mg.

30. The method of claim 23 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of bupropion.

31. The method of claim 23 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, is administered together with a pharmaceutically acceptable carrier.

32. The method according to claim 23 wherein (+)-bupropion is administered as the hydrochloride salt.

20 33. The method of claim 23 wherein (+)-bupropion is administered in a sustained release or controlled release formulation.

25 34. A method of treating a disorder selected from the group consisting of bipolar disorders, attention-deficit disorders, conduct disorders, psycho-sexual dysfunction, bulimia, eating disorders and specific food craving which comprises administering to a human suffering from said disorder a therapeutically effective amount of (+)-bupropion, or a pharmaceutically acceptable salt therefore, substantially free of its (-)-stereoisomer.

35 35. The method of claim 34 wherein (+)-bupropion is administered by intravenously, transdermally, or orally.

36. The method of claim 35 wherein (+)-bupropion is administered orally as a tablet or a capsule.

- 24 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952

37. The method of claim 34 wherein the amount administered is from about 10 mg to about 750 mg.

38. The method of claim 37 wherein the amount administered is from about 50 mg to about 600 mg.

39. The method of claim 38 wherein the amount administered is from about 60 mg to about 450 mg.

10 40. The method of claim 34 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of bupropion.

15 41. The method of claim 34 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, is administered together with a pharmaceutically acceptable carrier.

20 42. The method according to claim 34 wherein (+)-bupropion is administered as the hydrochloride salt.

43. The method of claim 34 wherein (+)-bupropion is administered in a controlled or sustained release  
25 formulation.

44. A pharmaceutical composition which comprises a therapeutically amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its  
30 (-)-stereoisomer, and a pharmaceutically acceptable carrier.

45. The composition according to claim 44 wherein the amount is about 10 mg to about 750 mg.

35 46. The composition according to claim 44 which comprises (+)-bupropion hydrochloride.

- 25 -

SUBSTITUTE SHEET ( rule 26 )

CA 02318960 2000-07-25

WO 99/38502

PCT/US99/01952

47. The composition according to claim 46 wherein said composition is adapted for oral administration.

48. The composition according to claim 46 adapted for 5 intravenous delivery.

49. The composition according to claim 46 for use in a transdermal formulation.

10 50. The composition according to claim 46 for use as a transdermal patch.

51. The composition of claim 46 wherein said composition is a solid preparation.  
15

52. A sustained release formulation which comprises (+)-bupropion or a pharmaceutically acceptable salt thereof substantially free of its (-)-stereoisomer, and a pharmaceutically acceptable carrier.  
20

53. The sustained release formulation of claim 52 wherein said formulation is a tablet, capsule or gelcap.  
25

30

35

- 26 -

**SUBSTITUTE SHEET ( rule 26 )**